Rifampicin/imipenem combination in the treatment of carbapenem-resistant *Acinetobacter baumannii* infections

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Received 7 November 2005; returned 10 March 2006; revised 19 April 2006; accepted 2 June 2006

**Background:** In the setting of a large endemic of *Acinetobacter baumannii* infections, treatment of those due to carbapenem-resistant strains, susceptible only to colistin, has become a major problem in our hospital during the past years. Successful results have been reported using colistin, but clinical experience with this antibiotic is limited. In our experimental studies using these strains in a mouse pneumonia model, the best results were observed with a combination of rifampicin and imipenem.

**Methods:** From July 2000 to September 2001, we performed a pilot study with patients suffering from serious infections due to carbapenem-resistant *A. baumannii*. Patients were treated with a rifampicin/imipenem combination and followed up prospectively. Cultures were repeated during and after treatment, and *in vitro* activity of rifampicin was monitored. Genotyping of these strains was performed by means of PFGE.

**Results:** Ten patients were selected: four with ventilator-associated pneumonia, and six with other infections (one catheter-related bacteraemia, five surgical infections). Three patients died, two of whom were considered therapeutic failures. In five of the seven patients who were cured, other procedures were also performed such as surgical drainage or catheter removal. *In vitro* development of high resistance to rifampicin was shown in seven (70%). PFGE demonstrated that initial isolates and high-resistant strains belonged to the same clones.

**Conclusions:** The results of our study argue against the use of a rifampicin/imipenem combination for the treatment of carbapenem-resistant *A. baumannii* infections. However, combinations of rifampicin with other antibiotics merit further studies.

**Keywords:** *A. baumannii*, carbapenem resistance, antibiotic combinations

**Introduction**

The treatment of life-threatening infections due to carbapenem-resistant *Acinetobacter baumannii* strains, often susceptible only to colistin, poses a serious challenge to clinicians.\(^1\) Though some authors have reported successful results with the use of this antibiotic, clinical experience is limited.\(^2\)

Over the past years, our hospital has been suffering from a sustained endemic due to carbapenem-resistant *A. baumannii*.\(^3\)

In this setting, a mouse model of pneumonia caused by carbapenem-resistant *A. baumannii* was developed in our laboratory.\(^4,5\) The poor results obtained with colistin argued against its choice in the treatment of pneumonia. The best results were observed with rifampicin/imipenem and rifampicin/tobramycin combinations.\(^4,5\)

In the light of these results, we subsequently treated a series of patients with serious infections due to carbapenem-resistant *A. baumannii* with the combination of rifampicin and imipenem.
Their data were collected prospectively in order to assess the efficacy of this combination and to monitor the development of rifampicin resistance.

Materials and methods

Setting and patients

The study was carried out at the Hospital Universitari de Bellvitge, a 1000 bed teaching hospital for adult patients (July 2000–September 2001). Patients suffering from serious infections due to carbapenem-resistant A. baumannii isolates were prospectively identified and treated with rifampicin/imipenem combined therapy. Patients receiving therapy for <48 h or treated with other concomitant antibiotics with potential activity against carbapenem-resistant A. baumannii were excluded. Cultures were repeated during and after treatment whenever the relevant sites were easily accessible. In vitro activity of rifampicin was monitored against A. baumannii isolates obtained in these subsequent cultures.

Therapeutic protocol

The study was conducted as a pilot study in a non-comparative fashion and was approved by the Ethics Committee of our hospital. Written informed consent was obtained from patients or their legal representatives. The dose of imipenem was 2 g per day (500 mg, four times a day, intravenously); the dose of rifampicin was 600 mg/12 h by intravenous infusion.

Definitions

Serious infections included bacteremia or sepsis, ventilator-associated pneumonia (VAP), and intraabdominal or other organ-space infections. Underlying condition and severity of illness were defined according to McCabe classification and SAPS II score and source of infection according to the CDC criteria. Therapy was determined as the number of days of combined regimen. Overall mortality was defined as death during hospitalization. Death was considered related to A. baumannii infection when persistent signs or symptoms of infection were present at the time of death and/or when death occurred within 1 week of the beginning of antibiotic therapy without any other clear explanation. Therapeutic failure was considered if clinical findings worsened after 72 h of initiation of therapy or did not improve during the treatment period. Criteria of cure required the disappearance of symptoms and signs of infection, but not the microbiological eradication of the microorganism at the site of source of infection.

Microbiological methods

A. baumannii isolate identification and susceptibility testing was performed using commercial panels Neg Combo 1S from Walkaway system. Definitive identification was performed by their ability to grow at 44°C. MICs of antibiotics were confirmed by the Etest method. The MIC of imipenem was determined by an agar dilution method according to the NCCLS guidelines. Breakpoints for colistin were those defined by the French Society for Microbiology (susceptibility: MIC ≤ 2 mg/L).

Results

Among the 14 patients considered suitable for rifampicin and carbapenem therapy, 4 were excluded (1 was given antibiotic therapy for 24 h only and 3 additionally received colistin). Thus, 10 patients (9 in intensive care units) were given rifampicin/imipenem for a mean time of 12.1 days (6–24 days) and were considered evaluable cases (Table 1). The source of A. baumannii infection was VAP in four patients and others in the remaining six patients (one catheter-related bacteremia, five post-surgical infections). A. baumannii isolates from all patients belonged to two multiresistant clones named A and E, in vitro susceptible only to colistin (MICs of imipenem ≥32 mg/L; MICs of rifampicin 4–8 mg/L) (Table 2). As previously described, in vitro time–kill curves showed a synergic effect with the combination of rifampicin and imipenem.

Among patients with VAP managed with antibiotic therapy only, two patients were cured (Patients 1 and 3); a third patient (Patient 2) was cured after 9 days of therapy, but 1 week later developed primary bacteremia due to high-level rifampicin-resistant A. baumannii and died; and the fourth patient (Patient 4) was considered a therapeutic failure and died at 8 days of treatment. Among patients with other infections, one with an intraabdominal abscess secondary to pancreatic surgery (Patient 6) failed and died at 15 days of treatment, and the remaining five patients were cured, one with catheter-related bacteremia and removal of catheter (Patient 5) and four with surgical infections and concomitant surgical drainage (Patients 7–10) (Table 1). Overall, three patients died, two because of a therapeutic failure, including persistent clinical findings and positive cultures that identified high-level rifampicin-resistant A. baumannii, and seven were cured.

In vitro susceptibility testing of carbapenem-resistant A. baumannii strains successively isolated showed development of high-level rifampicin-resistant A. baumannii in seven patients (70%). In four cases high-level rifampicin-resistant A. baumannii appeared in successive samples collected at the site of the initial infection: Patients 4 and 6 with therapeutic failures already mentioned, and peritoneal samples in two other patients with intraabdominal abscesses obtained at 8 and 9 days of therapy (Patients 7 and 8). The remaining three patients (Patients 1, 2 and 5) developed catheter-associated infection or primary bacteremia unrelated to the initial source of infection, at 15, 7 and 21 days, respectively, after therapy. In three of these seven patients who developed high-level rifampicin-resistant A. baumannii, low-level rifampicin-resistant A. baumannii were subsequently found; in one patient high-level rifampicin-resistant A. baumannii and low-level rifampicin-resistant A. baumannii were identified concomitantly. PFGE performed in these strains demonstrated that low-level rifampicin-resistant A. baumannii and the following high-level rifampicin-resistant A. baumannii and further low-level rifampicin-resistant A. baumannii isolates belonged to the same clone (Table 1)

Discussion

In our setting of endemic carbapenem-resistant A. baumannii infections that were only susceptible to colistin, and in view of our experience in pneumonia models in mice, we thought that the rifampicin/imipenem combination might be the best therapeutic option. Although all carbapenem-susceptible
Rifampicin/imipenem versus carbapenem-resistant *A. baumannii*

Table 1. Characteristics and outcome of carbapenem-resistant *A. baumannii* infections treated with rifampicin + imipenem

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age/sex</th>
<th>Diagnosis</th>
<th>Ward /SAPSII</th>
<th>Rx (days)a</th>
<th>Evolution</th>
<th>Date</th>
<th>Sample Description</th>
<th>MICb</th>
<th>MICc</th>
<th>Clone</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>55/M</td>
<td>VAP</td>
<td>ICU/27</td>
<td>8</td>
<td>cured</td>
<td>22/01/01 BAL</td>
<td>BAL, bronchoalveolar lavage</td>
<td>&gt;256</td>
<td>8</td>
<td>E</td>
</tr>
<tr>
<td>2</td>
<td>63/M</td>
<td>VAP</td>
<td>ICU/35</td>
<td>9</td>
<td>died</td>
<td>15/12/00 blood</td>
<td>128, 4 A</td>
<td>256</td>
<td>256</td>
<td>A</td>
</tr>
<tr>
<td>3</td>
<td>47/M</td>
<td>VAP</td>
<td>ICU/25</td>
<td>10</td>
<td>cured</td>
<td>30/12/00 sputum brushing</td>
<td>&gt;256, 8 A</td>
<td>256</td>
<td>4</td>
<td>ND</td>
</tr>
<tr>
<td>4</td>
<td>80/M</td>
<td>VAP</td>
<td>ICU/33</td>
<td>8</td>
<td>died</td>
<td>12/06/01 BAL</td>
<td>&gt;256, 8 E</td>
<td>256</td>
<td>256</td>
<td>E</td>
</tr>
<tr>
<td>5</td>
<td>52/F</td>
<td>catheter bacteraemia</td>
<td>ICU/35</td>
<td>6</td>
<td>therapeutic failure</td>
<td>18/06/01 sputum</td>
<td>&gt;256, 256 E</td>
<td>256</td>
<td>8</td>
<td>E</td>
</tr>
<tr>
<td>6</td>
<td>39/F</td>
<td>intraabdominal abscess</td>
<td>ICU/44</td>
<td>15</td>
<td>die(surgical drainage)</td>
<td>17/08/01 peritoneal fluid</td>
<td>&gt;256, 8 E</td>
<td>256</td>
<td>256</td>
<td>E</td>
</tr>
<tr>
<td>7</td>
<td>58/M</td>
<td>intraabdominal abscess</td>
<td>ICU/36</td>
<td>13</td>
<td>cured(surgical drainage)</td>
<td>27/03/01 abscess</td>
<td>64, 6 A</td>
<td>256</td>
<td>256</td>
<td>E</td>
</tr>
<tr>
<td>8</td>
<td>72/M</td>
<td>intraabdominal abscess</td>
<td>ICU/35</td>
<td>24</td>
<td>cured(surgical drainage)</td>
<td>24/05/00 abscess</td>
<td>&gt;256, 8 E</td>
<td>256</td>
<td>256</td>
<td>E</td>
</tr>
<tr>
<td>9</td>
<td>21/M</td>
<td>empyema</td>
<td>ICU/40</td>
<td>6</td>
<td>cured (thoracic drainage)</td>
<td>17/09/01 pleural effusion</td>
<td>128, 8 ND</td>
<td>64</td>
<td>6</td>
<td>A</td>
</tr>
<tr>
<td>10</td>
<td>65/M</td>
<td>arthroplasty hip infection</td>
<td>non-ICU/ND</td>
<td>22</td>
<td>cured (surgical drainage)</td>
<td>27/03/01 wound</td>
<td>64, 8 A</td>
<td>64</td>
<td>8</td>
<td>A</td>
</tr>
</tbody>
</table>

VAP, ventilator-associated pneumonia; ND, not done; BAL, bronchoalveolar lavage.
aLength of treatment.
bMIC of imipenem.
cMIC of rifampicin.

Table 2. Antibiotic susceptibility patterns of *A. baumannii* clones isolated at the beginning of the study (MICs in mg/L)

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Clone E</th>
<th>Clone A</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ticarcillin</td>
<td>&gt;256 (R)</td>
<td>&gt;256 (R)</td>
</tr>
<tr>
<td>Piperacillin</td>
<td>&gt;256 (R)</td>
<td>&gt;256 (R)</td>
</tr>
<tr>
<td>Ampicillin/sulbactam (2:1)</td>
<td>256/128 (R)</td>
<td>&gt;256/128 (I/R)</td>
</tr>
<tr>
<td>Ceftazidime</td>
<td>&gt;256 (R)</td>
<td>16–&gt;256 (I/R)</td>
</tr>
<tr>
<td>Cefepime</td>
<td>&gt;256 (R)</td>
<td>&gt;256 (R)</td>
</tr>
<tr>
<td>Imipenem</td>
<td>&gt;256 (R)</td>
<td>64–&gt;256 (R)</td>
</tr>
<tr>
<td>Meropenem</td>
<td>&gt;256 (R)</td>
<td>128–&gt;256 (R)</td>
</tr>
<tr>
<td>Gentamicin</td>
<td>&gt;256 (R)</td>
<td>&gt;256 (R)</td>
</tr>
<tr>
<td>Tobramycin</td>
<td>8–64 (R)</td>
<td>&gt;256 (R)</td>
</tr>
<tr>
<td>Amikacin</td>
<td>&gt;256 (R)</td>
<td>&gt;256 (R)</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>&gt;32 (R)</td>
<td>&gt;32 (R)</td>
</tr>
<tr>
<td>Colistin</td>
<td>0.5–64 (S/R)</td>
<td>0.5 (S)</td>
</tr>
<tr>
<td>Rifampicin</td>
<td>4–8 (LR)</td>
<td>4–8 (LR)</td>
</tr>
</tbody>
</table>

R, resistant; LR, low resistant; I, intermediate; S, susceptible.

*A. baumannii* and carbapenem-resistant *A. baumannii* strains we tested showed moderate resistance to rifampicin (MICs 4–8 mg/L), in our model rifampicin at high doses, equivalent to doses of 20 mg/kg/day in humans, provided successful pharmacodynamic parameters and better results than colistin against pneumonia due to carbapenem-susceptible *A. baumannii* and carbapenem-resistant *A. baumannii*. Similar results have been reported by other authors. While we did not detect an increase of rifampicin resistance in these experimental studies, we assumed that monotherapy with rifampicin could not be considered and therefore studied the effect of several combinations; of note, we found that the rifampicin/imipenem combination was additive in ‘killing’ curves and significantly more effective than rifampicin alone against clone E carbapenem-resistant *A. baumannii* pneumonia. Although a non-comparative study has some limitations, we believed that it was clinically important to apply and confirm in patients with serious infections due to carbapenem-resistant *A. baumannii* strains the information provided by our experimental studies.

In the study, a small sample of patients was treated with a rifampicin/imipenem combination. Of note, three of the four episodes of VAP were cured with this antibiotic regimen. Among patients with other infections, five were cured, although concomitant non-antibiotic treatments such as surgical drainage and device removal may have been decisive in this outcome. Overall, the crude mortality rates of 30% may be considered acceptable and within the range of figures usually reported. However, closer analysis shows that two of these cases were evaluated...
as therapeutic failures and died, and in both cases mortality was considered directly related to infection and ineffective antibiotic therapy.

It is difficult to establish whether the efficacy of rifampicin/imipenem we observed in our patients was due to the activity of rifampicin alone or was provided by an additive or synergic effect of the combination. In any case, the frequent development of high-level rifampicin-resistant *A. baumannii*, and the potential risk that this resistance determined therapeutic failure, should be considered as a strongly negative effect of this combination. PFGE studies demonstrated that high-level rifampicin-resistant *A. baumannii* belonged to the same clone as isolates found before the beginning of therapy. This resistance reverted in three cases in which follow-up of isolates was possible and no spread of high-level rifampicin-resistant *A. baumannii* between patients was detected.

Imipenem at usual human doses could not achieve sustained serum levels higher than the MIC for carbapenem-resistant *A. baumannii* (MIC ≥ 64 mg/L) and accordingly it was unable to prevent the development of high-level rifampicin-resistant *A. baumannii*. When we chose the rifampicin/imipenem combination to treat our patients, we based our criteria on the antibiotic’s efficacy recorded in the experimental model, but we did not pay sufficient attention to the non-favourable pharmacokinetic profile of these antibiotics in combination for the prevention of resistance.

Our results argue against the use of the rifampicin/imipenem combination for the treatment of carbapenem-resistant *A. baumannii* infections. However, the possible usefulness of rifampicin in other combinations should be further explored. The antibiotic chosen for administration with rifampicin in combination should itself have good *in vitro* activity against carbapenem-resistant *A. baumannii*. In the setting of our carbapenem-resistant *A. baumannii* strains, only colistin appears to offer this alternative. In fact, colistin should be considered a therapeutic option for these infections, since successful results have been reported. Whether the rifampicin/colistin combination provides better results than colistin alone and the extent to which colistin prevents the development of high rifampicin resistance are points that should be investigated further.

### Transparency declarations
None to declare.

### References